PATENT COOPERATION TREA /

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15529-WO-02	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL2004/000699	International filing date *(day/month/year)* 29.07.2004	Priority date *(day/month/year)* 31.07.2003
International Patent Classification (IPC) or national classification and IPC G01N33/68		
Applicant PRIOSENSE, LTD. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the International application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.05.2005	09.11.2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000699

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-39 as originally filed

   Claims, Numbers

   1-57 as originally filed

   Drawings, Sheets

   1/7-7/7 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-47(partially) and 55,56(partially)

because:

☒ the said international application, or the said claims Nos. 1-38 and 56 with respect to IA relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-9(partially),11-17(partially), 21-37(partially),39-47(partially) and 55,56(partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9(partially), 10(complete), 11-17(partially), 18-20(complete), 21-37(partially), 38(complete), 39-47(partially), 48-54(complete), 55, 56(partially) and 57(complete) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-10,18-20,22-30,38,43,44,47-54,57
	No:	Claims	1,11-17,21,31-37,39-42,45,46,55,56
Inventive step (IS)	Yes:	Claims	18,38,57
	No:	Claims	1-17,19-37,39-56
Industrial applicability (IA)	Yes:	Claims	39-55,57
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III.

1. The subject-matter of claims 1, 21, 39, 55 und 56 have only be partially searched. Consequently, an opinion with respect to patentability will only be given for an immunoglobulin light chain (LC) as a beta-sheet protein.

2. Claims 1 to 38 and 56 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT). The reason is that the term "providing" of present claim 1(a) could include a surgical step.

Re Item IV.

The separate inventions/groups of inventions are:

Group I: claims 1-9(partially), 10(complete), 11-17(partially), 18-20(complete), 21-37(partially), 38(complete), 39-47(partially), 48-54(complete), 55, 56(partially) and 57(complete)
A method for the diagnosis of a neurodegenerative disorder in a mammalian subject, by concentrating the sample first, then adding a IgG light chain (LC) protein to start aggregation of a marker molecule for said disorder and measuring aggregate formation.

Group II: claims 1-9(partially), 11-17(partially), 21-37(partially), 39-47(partially), 55, 56(partially)
A method for the diagnosis of a neurodegenerative disorder in a mammalian subject, by concentrating the sample, adding a human Bence Jones (BJ) protein to start aggregation of a marker molecule for said disorder and measuring aggregate formation.

Group III: claims 1-9(partially), 11-17(partially), 21-37(partially), 39-47(partially), 55, 56(partially)
A method for the diagnosis of a neurodegenerative disorder in a mammalian subject, by concentrating the sample, adding a recombinant PrP protein to start aggregation of a marker molecule for said disorder and measuring aggregate

formation.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The arguments of the applicant brought forward in his letter of reply have been taken into consideration. However, the objection under lack of unity is maintained for the following reasons:
The present application discloses a method for the diagnosis of a neurodegenerative disorder in a mammalian subject, by first concentrating a body fluid sample, adding a protein with a **beta-sheet structure**, (such as IgG light chain (LC) protein, Bence Jones protein or recombinant PrP protein), to start aggregation of a marker molecule for said disorder and measuring the aggregate formation.
The prior art mentions several methods for the diagnosis of neurodegenerative disorders in mammals starting from a body fluid, concentrating proteins comprised in the sample and detecting possible marker proteins after forming aggregates by using for example a monoclonal antibody. EP0854364 (D3) for example discloses such a method concentrating from a body fluid inter alia a protein associated with neuro-degenerative disorders (see abstract, col. 3, lines 20 to 30). Antibodies against PrP are mentioned that first bind to the protein before a second antibody is used to allow the detection of PrP as a marker indicative of a particular neuro-degenerative disorder (see col. 4, lines 45 to 53). The antibody binding the PrP has a beta-sheet structure and induces aggregation due to its Y-shaped form. Due to the broad wording of claim 1, D3 is considered to be detrimental to the novelty of the subject-matter of said claim. WO 02/33420 (D2) refers to a urine test for the diagnosis of prion diseases (see abstract). It detects PrPsc in a urine sample of a patient, concentrates the proteins in said sample by dialysing and precipitating it and uses a monoclonal antibody having a beat-sheet structure for the detection of PrPsc thereby aggregating it due to its Y-shaped structure (see page 5, line 1 to page 6, third para.). For the same reasons as outlined above D2 is considered to be detrimental to the novelty of the subject-matter of claim 1.

In the light of the prior art, the problem underlying the present application can be seen as the provision of further diagnostic tests for neurodegenerative disorders of patients by using further beta-sheet proteins.

The solution can be summarised as the provision of IgG light chain (LC) protein, Bence Jones protein or recombinant PrP protein all belonging to proteins having a beta-sheet structure.

However, the use of one beta-sheet protein as an amplifier for PrP aggregation, namely recombinant PrPsc, was already known from the prior art (see WO-A-0204954 (D1), page 4, lines 16 to 19). In summary, D2 and D3 are considered to destroy the linking unit of the different methods used, namely that a beat-sheet protein induces aggregation of a marker protein for neuro-degenerative disorders. It is admitted that this novelty objection can only be raised due to the unclear and functional wording of claim 1 c, in particular. But nevertheless since antibodies contain beta-sheet structures (see IgG light chain, claimed in the present application) and cause aggregation due to their Y-shaped structure, the objection is justified. Even if the method of claim 1 would be novel over D2 and D3, it does not appear to be inventive for the following reasons: D3 is considered to be the closest prior art. Said document discloses a diagnostic method for prion diseases by using a urine sample, concentrating said sample using a solid material, such as calcium phosphate (see col. 3, line 20 to col. 4, line 12). The 10000 x times concentrated marker protein can then either by visualised directly by electron microscopy due to the tubulofilamentous structure present or indirectly by using additional specific antibodies binding to said structures and increasing the size of the complexes by aggregation (see col. 4, lines 13 to 58). By using PrPsc in the present application the sensitivity of the test might be further increased due to the aggregation forming activity of said protein with respect to PrP. The obvious problem to be solved by the present application was thus to further increase the sensitivity of diagnostic method. However, D1 teaches that PrPsc induces aggregation formation of PrP proteins (see page 4, lines 16 to 19). Consequently, the skilled person was well aware of PrPsc being a beta-sheet protein inducing PrP aggregation which can be easily measured. In addition, no other technical feature can be distinguished which in the light of the prior art could be regarded as a special common technical feature linking the three different methods mentioned above. Thus, there appears still no single inventive concept being present underlying the plurality of different inventions in the sense of Rule 13.2 PCT.

Consequently, there is a lack of unity and the different inventions not belonging to a common inventive concept are formulated as different groups of inventions pursuant to Art. 17(3)(a) PCT.

Re Item V.

The following documents are referred to in this communication:

D1: WO 02/04954 A
D2: WO 02/33420 A
D3: EP0854364

1. Claim 1 refers to a method for the diagnosis of a neurodegenerative disorder in a mammalian subject, by first concentrating a body fluid sample, adding a protein with a beta-sheet structure, such as IgG light chain (LC) protein, Bence Jones protein or recombinant PrP protein, to start aggregation of a marker molecule for said disorder and measuring the aggregate formation.

D1 discloses a method and a kit for the diagnosis of neurodegenerative disorders in body fluids wherein a marker protein for spongiform encephalopathy, namely PrPsc is after a concentration step first amplified by adding recombinant PrP before the formed aggregates are measured (see abstract, page 1, lines 21 to 29, page 4, line 29 to page 13, line 7). It also mentions the use of one beta-sheet protein as an amplifier for PrP aggregation, namely recombinant PrPsc, was (see page 4, lines 16 to 19).

WO 02/33420 (D2) refers to a urine test for the diagnosis of prion diseases (see abstract). It detects PrPsc in a urine sample of a patient, concentrates the proteins in said sample by dialysing and precipitating it and uses a monoclonal antibody having a beat-sheet structure for the detection of PrPsc thereby aggregating it due to its Y-shaped structure (see page 5, line 1 to page 6, third para.). The antibody binding the PrP has a beta-sheet structure and induces aggregation due to its Y-shaped form. Due to the broad wording of claim 1, D2 is considered to be detrimental to the novelty of the subject-matter of said claim. Moreover, it is considered to be detrimental to the novelty of the subject-matter of claims 11 to 17, 21, 31 to 37, 39 to 42, 45, 46, 55 and 56.

EP0854364 (D3) for example discloses such a method concentrating from a body fluid inter alia a protein associated with neuro-degenerative disorders (see abstract, col. 3, lines 20 to 30). Antibodies against PrP are mentioned that first bind to the protein before

a second antibody is used to allow the detection of PrP as a marker indicative of a particular neuro-degenerative disorder (see col. 4, lines 45 to 53). The antibody binding the PrP has a beta-sheet structure and induces aggregation due to its Y-shaped form. Due to the broad wording of claim 1, D3 is considered to be detrimental to the novelty of the subject-matter of said claim. Moreover, it is considered to be detrimental to the novelty of the subject-matter of claims 11 to 17, 21, 31 to 37, 39 to 42, 45, 46, 55 and 56.

Consequently, the subject-matter of claims 1, 11 to 17, 21, 31 to 37, 39 to 42, 45, 46, 55 and 56 is not novel and does not comply with the requirements of Art. 33(2) PCT.

2. Even if the applicant were to incorporate a new process step into independent claim 1 in order to render the subject-matter novel over D2 or D3 the present application would not meet the requirements of Articles 33(3) PCT, because the subject-matter of such a claim 1 would appear not to involve an inventive step for the following reasons:
D3 is considered to be the closest prior art. Said document discloses a diagnostic method for prion diseases by using a urine sample, concentrating said sample using a solid material, such as calcium phosphate (see col. 3, line 20 to col. 4, line 12). The 10000 x times concentrated marker protein can then either by visualised directly by electron microscopy due to the tubulofilamentous structure present or indirectly by using additional specific antibodies binding to said structures and increasing the size of the complexes by aggregation (see col. 4, lines 13 to 58). By using PrPsc in the present application the sensitivity of the test might be further increased due to the aggregation forming activity of said protein with respect to PrP. The obvious problem to be solved by the present application was thus to further increase the sensitivity of diagnostic method. However, D1 teaches that PrPsc induces aggregation formation of PrP proteins (see page 4, lines 16 to 19). Consequently, the skilled person was well aware of PrPsc being a beta-sheet protein inducing PrP aggregation which can be easily measured. Consequently, presence of an inventive step could not be acknowledged (Art. 33(3) PCT).

However, a restriction of independent claim 1 to the subject-matter of claim 18 or 38 would render the claim novel and inventive for the following reasons:

IgG LC protein was never used before for the amplification of PrPsc protein. Moreover, it leads to an aggregation of PrPsc like the addition of recombinant PrP. This effect appears neither to be obvious from any of the available prior art documents nor directly derivable. Consequently, presence of an inventive step could be acknowledged (Art. 33(3) PCT). The same arguments apply for the subject-matter of claim 10, 30, 48 and 57.

3. For the assessment of the present claims 1 to 38 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in diagnostic treatment, but may allow, however, claims to a known compound for first use in diagnostic treatment and the use of such a compound for the manufacture of a diagnostic preparation for a new diagnostic assay.

4. Further matter:

4.1 The terms "suitable means" and protein with a "beta-sheet structure" used inter alia in claim 1 are vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT. the same applies to terms "substance having affinity to a specific compound in said aggregate" and "specific dye" inter alia used in claim 5.

4.2 The scope of present claims 1 and 21 appear to overlap rendering the scope of protection of said two claims unclear (Art. 6 PCT).